Regarding the Amendments to the Claims

Support for the claim amendments can be found throughout the specification. In particular, the amendment to claims 1 and 2 to recite "human" is supported, for example, in Figures 2 and 3. The amendment to claim 4 to recite "or" instead of "and" is supported, for example, by claim 3 and at page 7, lines 7-9. The amendment to claims 11 and 12 to delete the term "non-human" and to insert the term "cell" is supported, for example, at page 11, lines 8-11, and by claim 11, as originally filed. The amendment to claim 14 to recite particular hybridization conditions is supported, for example, at page 12, lines 8-10. Claim 7 also has been amended to delete multiple claim dependencies and to delete the recitation of "preferably;" the amendment deleting reference to particular substitutions, e.g., "S182T, K198N," etc., was made due to new claim 49 (discussed below). The amendment to claim 3 to delete the term "or involving" was made to address the Examiner's concern with the term and does not pertain to patentability. The amendment to claim 5 was made to delete multiple claim dependencies and does not pertain to patentability. The amendment to claim 8 was made to correct a typographical error and does not pertain to patentability. Claim 9 has been amended to delete multiple claim dependencies and to address the Examiner's concern with the term "which" and does not pertain to patentability. Claim 14 has also been amended to delete multiple claim dependencies and does not pertain to patentability. Claim 48 has been amended in response to the Examiner's request to conform the claim with elected group I claims. Thus, as the amendments to the claims are supported by the specification or were made to address various informalities, no new matter has been added. Accordingly, entry of the claim amendments is respectfully requested.

Regarding the New Claims

New claim 49, directed to "the nucleic acid molecule of claim 7, wherein said combination of substitutions in positions 182 is from S to T, 198 from K to N, and 201 from T to R; positions 201 is from T to R and 223 from F to V; or in positions 16 is from W to C, 201 from T to R, and 223 from F to V," is supported throughout the specification. In particular, claim 7, as filed, recites the amino acid substitutions now recited in claim 49. New claims 50 and 51, directed to oligonucleotides of claim 14, 12 to 50 and 15 to 24 nucleotides in length, respectively, is supported, for example, at page 12, lines 12-14. Thus, claims 49 to 51 do not add new matter. Accordingly, entry of claims 49 to 51 is respectfully requested.

I. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The rejection of claims 1 to 12, 14 and 48 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement is respectfully traversed. The Examiner indicates that the specification "while being enabling for polynucleotide of SEQ ID NO:41 and oligonucleotides of represented by SEQ ID NOs:3-4, 7, 16-18, 20, 23, 25-26, 29-30, and 39-40 for screening missense mutation in RHD gene" allegedly does not provided enablement for the full scope of claims 1 to 12, 14 and 48.

The specification adequately enables the claims as originally filed. Nevertheless, solely in order to further prosecution of the subject application, claims 1 and 2 have been amended to recite that the nucleic molecules encode "human" Rhesus D antigen contributing to or indicative of a weak D phenotype.

A proper analysis for enablement under 35 U.S.C. §112, first paragraph is whether one skilled in the art could make and use the claimed invention without undue experimentation. In the present case, one skilled in the art could practice the invention of claims 1 to 12, 14 and 48 without undue experimentation.

First, the Office Action mischaracterizes the meaning of the claims by stating at page 5, second full paragraph, that the specification discloses "only one polynucleotide of SEQ ID NO:41 that encodes a Rhesus D antigen carrying one or more missense mutations which contribute to weak D phenotype." [Emphasis added] The claims, however, as exemplified by claim 1, are directed to a "nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of a weak D phenotype," and as further discussed below the specification exemplifies 22 different nucleic acid molecules that encode a human Rhesus D antigen contributing to or indicative of a weak D phenotype.

In addition, the claims have been amended to recite "human" Rhesus D antigen. In this regard, if present, the human RHD gene is highly conserved among humans. Generally, in humans having an intact RHD gene, nucleotide sequence homology exceeds 90%, more typically 99% or greater. Furthermore, the nucleotide sequences of other human RHD alleles can be easily identified using routine molecular biology gene cloning via nucleic acid hybridization screening protocols and subsequent sequencing that have long been routine in the art. As discussed below, such newly identified human RHD alleles can then be subsequently analyzed

for the presence of a mutation contributing to or indicative of a weak D phenotype using routine methods disclosed in the specification and known in the art.

Moreover, the statement in the Office Action at page 5, paragraph 2, that "claims 1-9, the said nucleic acid molecule can encompass an infinite number of polynucleotide that may or may not encode a Rhesus D antigen," is erroneous. Rather, claims 1 and 2 recite that the nucleic acid molecule encodes "a human Rhesus D antigen contributing to or indicative of a weak D phenotype" and, therefore, the claimed nucleic acid molecules must encode "a human Rhesus D antigen contributing to or indicative of a weak D phenotype." Thus, contrary to the Office Action, it is not possible that the nucleic acid of claims 1 to 9 encompass polynucleotides that do not encode Rhesus D antigen.

Thus, as human RHD alleles are highly conserved among human individuals, are identifiable using routine techniques known in the art and can be screened for the presence of mutations contributing to or indicative of a weak D phenotype using routine assays and, furthermore, that nucleic acids that do not encode Rhesus D antigen are not included in claims 1 and 2, Applicants need not disclose additional RHD gene sequences in order to adequately enable the claims. As such, it would be improper to limit Applicant's claims to SEQ ID NO:41.

As to the assertion in the Office Action at page 5, third full paragraph, that "there is no guidance in the specification as to which position within the full length of said nucleic acid molecule that after substitution, deletion or insertion will retain both structure and function similar to SEQ ID NO:41 or contribute to weak D phenotype," the specification exemplifies numerous nucleic acid molecules with missense mutations encoding human rhesus D antigen that contribute to or are indicative of the weak D phenotype. For example, the specification discloses missense mutations that contribute to or are indicative of the weak D phenotype at positions 8, 29, 48, 340, 446, 544, 594, 602, 658, 667, 809, 819, 826, 830, 845, 880, 885, 919, 1016, 1154 and 1177 of RHD gene (page 8, lines 5-12). Such missense mutations are within either the transmembrane or intracellular region of Rhesus D antigen (page 6, lines 15-18). The specification also discloses a gene conversion indicative of weak D phenotype, exons 6 to 9 replaced with the corresponding exons of RHCE (page 6, lines 13-14). Thus, in view of the fact that the specification exemplifies numerous particular nucleic acids encoding human rhesus D antigen that contribute to or are indicative of the weak D phenotype as well as their general location, the skilled artisan would know the identity of many nucleic acid molecules encoding

human rhesus D antigen that contribute to or are indicative of the weak D phenotype. As such, the skilled artisan need only screen for the presence of the disclosed sequences in order to identify such a nucleic acid molecule.

As to identifying additional RHD missense mutations that contribute to or are indicative of the weak D phenotype, the specification discloses general assays for identifying patients with the weak D phenotype. For example, the specification discloses that blood samples may be analyzed for expression of antigen D using PCR-RFLP (page 28, lines 5-9). To identify nucleic acid molecules with missense mutations, the specification discloses that samples with weak D expression can subsequently be analyzed for missense mutations by nucleotide sequencing or by PCR-RFLP or RH PCR-SSP (see, for example, page 8, lines 17-24, and page 29, lines 9-25). To identify RHD gene conversion involving exons 6 and 9 replaced with the corresponding region of RHCE gene, the specification discloses that samples with weak D expression can be analyzed for by sequencing with primers specific for RHCE and RHD; detecting the presence of RHCE sequences in the RHD gene indicates the presence of the gene conversion (page 29, line 25, to page 30, line 5). Nucleotide sequencing, PCR-RFLP and RH PCR-SSP for detecting sequence mutations, among other assays for detecting RHD gene alleles (e.g., Smythe *et al.*, Blood 87:2968 (1996)) are well known in the art and are routine. Furthermore, the specification discloses that the location of the missense mutations, as recited in claim 1, is in the "transmembrane and/or intracellular regions." Thus, the skilled artisan would know to look in this region of newly identified RHD alleles for missense mutations that contribute to or are indicative of the weak D phenotype.

Accordingly, contrary to the assertion in the Office Action, the skilled artisan need not know *a priori* or be able to "predict" each and every missense mutation in human rhesus D antigen that contributes to or is indicative of the weak D phenotype. Rather, the skilled artisan, using routine assays disclosed in the specification would simply screen a blood sample from a patient for an RHD missense mutation in its transmembrane or intracellular region, or a conversion in the gene encoding Rhesus D antigen involving exons 6 and 9 replaced with the corresponding region of RHCE gene, to identify nucleic acid molecules encoding a human Rhesus D antigen contributing to or indicative of weak D phenotype. Thus, in view the detailed guidance in the specification for identifying other RHD gene mutations that contribute to or are indicative of the weak D using routine assays known in the art, undue experimentation would not

be required to identify other nucleic acid molecules encoding human Rhesus D antigen contributing to or indicative of the weak D phenotype as in claims 1 and 2.

In regard to the grounds for rejection due to alleged unpredictability of determining specificity of hybridization probes, claim 14 has been amended to recite particular hybridization conditions, 0.1X SSC, 0.1% SDS at 65^0 C hybridization and washing conditions. In view of the amendment, the claimed oligonucleotides would preferentially hybridize to a portion of the nucleic acid of claims 1 or 2 comprising at least one missense mutation or complementary portion thereof or hybridizing to a region involving the breakpoint of the gene conversion of claim 2. As such, this grounds for rejection is believed moot.

In sum, in view of the guidance in the specification and using routine assays known in the art, the skilled artisan could practice the claimed invention without undue experimentation. As such, amended claims 1 to 12, 14 and 48 are adequately enabled and Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph as allegedly lacking enablement be withdrawn.

The rejection of claims 1 to 12, 14 and 48 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed had possession of the claimed invention, is respectfully traversed. The Examiner indicates that allegedly the specification does not provide an adequate written description of the nucleic acid molecules, vectors, methods oligonucleotides and kits of claims 1 to 12, 14 and 48.

The specification provides an adequate written description of the claims, as originally filed. Nevertheless, solely in order to further prosecution of the subject application, amended claims 1 and 2 now recite that the nucleic molecules encode "human" Rhesus D antigen contributing to or indicative of a weak D phenotype. The grounds for rejection will therefore be addressed in respect to the amended claims.

As discussed above, the specification exemplifies 22 different nucleic acid molecules that encode a human Rhesus D antigen contributing to or indicative of a weak D phenotype. For example, the specification discloses nucleic acid molecules encoding RHD genes with missense mutations at positions 8, 29, 48, 340, 446, 544, 594, 602, 658, 667, 809, 819, 826, 830, 845, 880, 885, 919, 1016, 1154 and 1177 and an RHD gene conversion in which exons 6 to 9 replaced with

the corresponding exons of RHCE which contribute to or are indicative of the weak D phenotype. Thus, in view of the number of different nucleic acid molecules that encode a human Rhesus D antigen contributing to or indicative of a weak D phenotype disclosed in the specification, a representative number of species is disclosed to enable the genus of nucleic acid molecules as claimed.

Furthermore, as discussed above, human RHD is highly conserved among humans that have the gene. Moreover, the sequence of many human RHD alleles was known at the time of the invention. In this regard, the Examiner's attention is directed to Flegel *et al.*, (Transfus. Med. 8:281 (1998)), submitted herewith Exhibit A. Exhibit A indicates that numerous RHD alleles were known at the time of the invention (see, for example, Table 4, which lists PCR setups for detecting numerous particular RHD alleles). Thus, given the high homology of human RHD and that numerous RHD alleles were known at the time of the invention, the nucleotide sequences of other human RHD alleles will be predicted to share significant sequence homology with SEQ ID NO:41. The skilled artisan would therefore be apprised of the sequences that are human RHD genes or could readily ascertain whether a given sequence is a human RHD gene using routine sequencing protocols. As such, an adequate written description of human RHD sequences is provided.

As to the assertion in the Office Action at page 7, last paragraph, that "there is no description about the structure associated with function of 'any nucleic acid' mentioned above, that is critical for screening blood of donor and recipient for the presence of one or more missense mutation in the Rh D antigen," to the contrary, the specification discloses that RHD gene missense mutations are located in the transmembrane or intracellular regions and that such mutations appear to affect expression of Rh complex involving RhD (see, for example, page 4, lines 10-14; page 4, lines 15-19 and Table 7). Moreover, claim 1 recites that the missense mutation is in its "transmembrane and/or intracellular regions." Thus, given the location of the missense mutations in the Rhesus D antigen and the fact that the region has a well defined function, there is no objective basis for the assertion that there is no description of the structure associated with function for screening of donor and recipient for one or more missense mutations in Rhesus D antigen. Accordingly, this grounds for rejection should properly be withdrawn.

As to the grounds for rejection in the Office Action at page 8, second full paragraph, relating to olgonucleotides and allegedly that "there is no description about the structure of any

'oligonucleotide'," Applicants respectfully disagree as the skilled artisan would know or could readily ascertain the olgonucleotides that would hybridize under stringent conditions, given that such conditions are disclosed in the specification (see, for example, page 12 of the specification which cites Sambrook *et al.* and Hames and Higgins, each of which describe stringent hybridization conditions). Particular oligonucleotides that specifically hybridize are exemplified in the specification, for example, SEQ ID NOs: 3, 4, 7, 16-18, 20, 23, 25, 26 29, 30, 39 and 40. Therefore, an adequate written description is provided for claim 14, prior to the present amendment.

Nevertheless, solely in order to further prosecution of the subject application, claim 14, as amended, now recites "0.1X SSC, 0.1% SDS at 65^0 C hybridization and washing conditions." Accordingly, in view of the amendment to claim 14 reciting specific hybridization and washing conditions, the grounds for rejection are believed moot.

In sum, in view of the number of species of nucleic acid molecules disclosed in the specification that are within the claims, the conservation of human RHD gene sequences and the location of the missense mutations in RHD gene transmembrane or intracellular regions that lead to weak D phenotype, an adequate written description is provided for amended claims 1 to 12, 14 and 48. As such, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The rejection of claims 1 to 12, 14 and 48 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is respectfully traversed. The Examiner indicates that several terms in the rejected claims are ambiguous.

By the present amendment, the claims have been amended to address each of the grounds for rejection. In particular, claim 3 has been amended to delete "/or involving;" claim 4 has been amended to delete the recitation of "and" in the last line of the claims. Claim 7 has been amended to delete reference to the abbreviations and new claim 49 incorporates the changes to the abbreviations suggested by the Examiner. Claims 7 and 8 have been amended to delete the term "preferably;" claim 8 also has been amended to more clearly indicate the abbreviations, as suggested by the Examiner. Claim 9 has also been amended as suggested by the Examiner.

Claims 11 and 12 have been amended to recite "cell" as suggested by the Examiner. Claim 14 has been amended to recite particular hybridization conditions.

Thus, in view of the amendments, claims 1 to 12, 14 and 48 are clear and definite. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

III. REJECTIONS UNDER 35 U.S.C. §102 and 103(a)

The rejection of claims 1, 2, 9 and 14 under 35 U.S.C. §102(b) as allegedly anticipated by LeVan *et al.* (Blood 83:3098 (1994)) is respectfully traversed. The Examiner indicates that LeVan *et al.* allegedly describe "a polynucleotide (Accession number A46368) that encodes a Rhesus D antigen carrying one missense mutation at the amino acid position 218 which is within the amino acid position from 114 to 149 as recited in instant claim 2." LeVan *et al.* also allegedly describe that "the reference polynucleotide is genomic DNA" (claim 9) and "PCR primers which are oligonucleotides that hybridize under stringent conditions to a portion of the reference polynucleotide carrying missense mutation or the complementary thereof" (claim 14).

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (In re Spada, 15 USPQ 2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 2d 1566 (Fed. Cir. 1990).

Applicants first wish to point out that the author of the cited Blood article is actually Westhoff and Wylie (see page 3099 at the conclusion of the article). Accordingly, Applicants will address this cited article hereinafter as "Westhoff *et al.*"

Applicants also wish to point out that the alleged missense mutation at amino acid position 218 described by Westhoff *et al.* (Met) corresponds to amino acid 218 of the disclosed RHD gene (Met). Thus, contrary to the Examiner's statement in the Office Action, the amino acid position is not within amino acid position 114-149 of claim 2, but rather is within the amino acid position 179-225 of claim 2. Applicants respectfully request that the Examiner acknowledge the apparent erroneous statement made in the Office Action or clarify the statement for the prosecution record.

Westhoff *et al.* do not teach or suggest the claimed invention. For example, *inter alia*, Westhoff *et al.* do not describe a nucleic acid encoding a Rhesus D antigen carrying a missense mutation as compared to wild type as in claims 1 and 2. At most, the authors describe a

sequence which was deleted from nucleotides 940-1228. However, Westhoff *et al.* do not teach or suggest a nucleic acid molecule encoding a Rhesus D antigen with a missense mutation, nor a gene conversion involving exons 6 to 9, as recited in claim 2, let alone a missense mutation contributing to or indicative of the weak D phenotype. In this regard, the Office Action indicates that Westhoff *et al.* describe a missense mutation in RHD gene which results in a Met residue at position 218. However, to the contrary Westhoff *et al.* do not describe such a missense mutation because the Met residue at position 218 does not result from a missense mutation. In support of Applicants position, the Examiner's attention is directed to Cartron *et al.* (Transfus. Clin. Biol. 6:497 (1996)), submitted herewith as Exhibit B, in which the authors indicate that a previously described RHD gene sequence with Ile at position 218 resulted from a sequence error. In particular, the authors of Exhibit B state that "Position 218 is probably not affected since resequencing of D indicates presence of Met218 rather than Ile218 as previously described" (see Table 2 footnote +, which cites Kim *et al.* in Proc. Natl. Acad. Sci. USA 89:10925 (1992), which describes the nucleotide sequence thought to encode an Ile at position 218 instead of a Met at position 218). Exhibit B therefore demonstrates that a sequence error in Kim *et al.* resulted in an incorrect Ile residue at position 218 instead of the correct Met residue. Thus, the Rhesus D sequence described by Westhoff *et al.* does not include a missense mutation.

Accordingly, as Westhoff *et al.* do not describe a nucleic acid molecule encoding a human Rhesus D antigen including a missense mutation, let alone a missense mutation contributing to or indicative of the weak D phenotype, Westhoff *et al.* do not describe the nucleic acid molecule of claims 1, 2 and 9, or an oligonucleotide that hybridizes to such a nucleic acid molecule (claim 14). As such, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) over Westhoff *et al.* (Blood 83:3098 (1994)) be withdrawn.

The rejections of claims 1 to 3, 9 and 14 under 35 U.S.C. §102(b) as allegedly anticipated by Salvignol *et al.* (Biochem. Genet. 32:201 (1994)) is respectfully traversed. The Examiner cites two sequences, Accession numbers I37076 and I84434 in making the two rejections. The Examiner indicates that Salvignol *et al.* describe "a polynucleotide (Accession number I37076) that encodes a Rhesus D antigen carrying one missense mutation at the amino acid position 282 which is within the amino acid position 267 to 397 as recited in instant claim 2." Salvignol *et al.* is also indicated to describe "a polynucleotide (Accession number I84434) that encodes a Rhesus D antigen carrying at least one missense mutation .... at the amino acid position range from 114-

149 as recited in instant claim 2." Salvignol *et al.* further allegedly describe that "the reference polynucleotide is genomic DNA" (claim 9) and "oligonucleotides that hybridize to the reference polynucleotide comprising missense mutation or the complementary [or a] portion thereof" (claim 14).

Salvignol *et al.* do not teach or suggest the claimed invention. For example, *inter alia*, Salvignol *et al.* do not describe a nucleic acid molecule encoding a human Rhesus D antigen as required by amended claims 1 and 2. Rather, Accession number I37076 is a gorilla sequence and Accession number I84434 is a crab-eating macaque sequence. Furthermore, Salvignol *et al.* do not teach or suggest a nucleic acid encoding a human Rhesus D antigen with a missense mutation, let alone a missense mutation contributing to or indicative of the weak D phenotype. Accordingly, as Salvignol *et al.* do not describe a nucleic acid molecule as recited in the claims, Salvignol *et al.* can not anticipate claims 1 to 3, 9 and 14. As such, Applicants respectfully request that the rejections of claims 1 to 3, 9 and 14 under 35 U.S.C. §102(b) over Salvignol *et al.* (Biochem. Genet. 32:201 (1994); Accession numbers I37076 and I84434) both be withdrawn.

The rejection of claims 1 to 5, 9 and 14 under 35 U.S.C. §102(b) as allegedly anticipated by Salvignol *et al.* (Biochem. Genet. 32:201 (1994)) is respectfully traversed. The Examiner indicates that Salvignol *et al.* describe "a polynucleotide (Accession number I37075) that encodes a Rhesus D antigen carrying at least one missense mutation .... at the amino acid position range from 2-16, 114-149, 179-225 and 267-397 as recited in instant claim 2." Salvignol *et al.* also allegedly describe that "the reference polynucleotide is genomic DNA" (claim 9) and "oligonucleotides that hybridize under stringent conditions to the reference polynucleotide carrying missense mutation or the complementary thereof" (claim 14).

Applicants first note that the Accession number referenced in the Office Action, I37075, appears to be incorrect. The correct Accession number appears to be I37005. Applicants respectfully request that the Examiner confirm this apparent error.

Salvignol *et al.* (Accession number I37005) do not teach or suggest the claimed invention. For example, *inter alia*, Salvignol *et al.* do not describe a nucleic acid molecule encoding a human Rhesus D antigen as required by amended claims 1 and 2. Rather, Accession number I37005 is a chimpanzee sequence. Furthermore, Salvignol *et al.* do not teach or suggest a nucleic acid molecule encoding a human rhesus D antigen with a missense mutation, let alone a

missense mutation contributing to or indicative of the weak D phenotype. Accordingly, as Salvignol *et al.* do not describe a nucleic acid molecule as recited in the claims, Salvignol *et al.* can not anticipate claims 1 to 5, 9 and 14. As such, Applicants respectfully request that the rejection of claims 1 to 5, 9 and 14 under 35 U.S.C. §102(b) over Salvignol *et al.* (Biochem. Genet. 32:201 (1994); Accession number I37005) be withdrawn.

The rejection of claims 1 to 4, 9 and 14 under 35 U.S.C. §102(b) as allegedly anticipated by Cherif-Zahar *et al.* (Proc. Natl. Acad. Sci. USA 87:6243 (1990)) is respectfully traversed. The Examiner indicates that Cherif-Zahar *et al.* describe "a polynucleotide (Accession number A30405) that encodes a Rhesus D antigen carrying at least one missense mutation .... at the amino acid position range from 179-225 as recited in instant claim 2." As to claim 3, Cherif-Zahar *et al.* are indicated to describe "the missense mutation in the reference polynucleotide cause by an amino acid substitution at position at 182, 198 and 223." As to claim 4, Cherif-Zahar *et al.* are indicated to describe "missense mutation in the reference polynucleotide causes by an amino acid substitution at position 182 to Thr, at position 198 to Asn, at position Val." As to claims 9 and 14, Cherif-Zahar *et al.* allegedly describe that "the reference polynucleotide is genomic DNA" and "oligonucleotides (primers) that hybridize to the reference polynucleotide or a portion thereof and the complementary thereof carrying missense mutation."

Cherif-Zahar *et al.* (Accession number A30405) do not teach or suggest the claimed invention. For example, *inter alia*, Cherif-Zahar *et al.* do not describe a nucleic acid molecule encoding a human Rhesus D antigen as required by amended claims 1 and 2. Rather, Accession number A30405 is an RHCE sequence. Furthermore, Cherif-Zahar *et al.* do not teach or suggest a nucleic acid molecule encoding a human rhesus D antigen with a missense mutation, let alone a missense mutation contributing to or indicative of the weak D phenotype. Accordingly, as Cherif-Zahar *et al.* do not describe a nucleic acid molecule as recited in the claims, Cherif-Zahar *et al.* can not anticipate claims 1 to 4, 9 and 14. As such, Applicants respectfully request that the rejection of claims 1 to 4, 9 and 14 under 35 U.S.C. §102(b) over Cherif-Zahar *et al.* (Proc. Natl. Acad. Sci. USA 87:6243 (1990)) be withdrawn.

The rejection of claims 10 to 12 and 14 under 35 U.S.C. §103(a) as allegedly unpatentable over LeVan *et al.* (correct cite is Westhoff *et al.*) in view of Salvignol *et al.* (Biochem. Genet. 32:201 (1994) or Cherif-Zahar *et al.* (Proc. Natl. Acad. Sci. USA 87:6243 (1990)) each in view of Sambrook *et al.* (Molecular Cloning, 1989, Cold Spring Harbor

Laboratory, CSH, NY, Ch. 17) is respectfully traversed. The Examiner indicates that the secondary reference of Sambrook *et al.* adds the limitations missing from the primary cited references as to claims 10 to 12 and 14, thereby allegedly rendering these claims obvious.

Claims 10 to 12 and 14 would not have been obvious in view of any of Westhoff *et al.*, Salvignol *et al.* or Cherif-Zahar *et al.* (Proc. Natl. Acad. Sci. USA 87:6243 (1990)) and Sambrook *et al.* alone, or in any combination.

As set forth above, Westhoff *et al.* do not describe a nucleic acid encoding a Rhesus D antigen carrying a missense mutation. Again, although the Office Action indicates that Westhoff *et al.* describe a missense mutation in RHD gene which results in a Met residue at position 218, Exhibit B (Cartron *et al.*, Transfus. Clin. Biol. 6:497 (1996)) discussed above indicates that this is incorrect. The authors indicate in Exhibit B that an RHD gene sequence previously described in Kim *et al.* (Proc. Natl. Acad. Sci. USA 89:10925 (1992)) had a sequence error; Ile at position 218 resulted from a sequence error and the correct sequence resulted in Met at position 218, as illustrated in Westhoff *et al.* Exhibit B therefore demonstrates that the sequence described by Westhoff *et al.* does not include a missense mutation. Furthermore, Westhoff *et al.* do not teach or suggest a nucleic acid molecule encoding a human RHD antigen having a missense mutation contributing to or indicative of the weak D phenotype.

Salvignol *et al.* do not describe a nucleic acid molecule encoding a human Rhesus D antigen as required by amended claims 1 and 2. Rather, Accession numbers I37076, I84434 and I37005 are gorilla, crab-eating macaque and chimpanzee sequences, respectively. Nor do Salvignol *et al.*, teach or suggest a nucleic acid molecule encoding a human RHD antigen having a missense mutation, let alone a missense mutation contributing to or indicative of the weak D phenotype.

Cherif-Zahar *et al.* do not describe a nucleic acid molecule encoding a human RHD antigen as in amended claims 1 and 2, rather, Accession number A30405 is an RHCE sequence. Nor do Cherif-Zahar *et al.*, teach or suggest a nucleic acid molecule encoding a human RHD antigen having a missense mutation, let alone a missense mutation contributing to or indicative of the weak D phenotype.

The secondary citation of Sambrook *et al.* fails to provide that which is missing from Westhoff *et al.*, Salvignol *et al.* and Cherif-Zahar *et al.* In particular, Sambrook *et al.* do not teach or suggest a nucleic acid molecule encoding a human Rhesus D antigen. Nor do Sambrook

et al. teach or suggest a nucleic acid molecule encoding a human RHD antigen having a missense mutation. Finally, Sambrook *et al.* do not teach or suggest a nucleic acid molecule encoding a human RHD antigen having a missense mutation contributing to or indicative of the weak D phenotype.

Thus, absent any teaching or suggestion of the invention of claims 10 to 12 and 14, the claims would not have been obvious at the time of the invention in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection of claims 10 to 12 and 14 under 35 U.S.C. §103(a) be withdrawn.

The rejection of claim 48 under 35 U.S.C. §103(a) as allegedly unpatentable over LeVan *et al.* (correct cite is Westhoff *et al.*), Salvignol *et al.* (Biochem. Genet. 32:201 (1994) or Cherif-Zahar *et al.* (Proc. Natl. Acad. Sci. USA 87:6243 (1990)) each in view of Sambrook *et al.* (Molecular Cloning, 1989, Cold Spring Harbor Laboratory, CSH, NY, Ch. 17) is respectfully traversed. The Examiner indicates that the secondary reference of Sambrook *et al.* adds the limitation missing from the primary cited references as to claim 48, thereby allegedly rendering claim 48 obvious.

Claim 48 depends from claim 14, which as set forth above, would not have been obvious in view of any of Westhoff *et al.*, Salvignol *et al.* or Cherif-Zahar *et al.* and Sambrook *et al.* alone, or in any combination.

Again, Westhoff *et al.* do not describe a nucleic acid encoding a Rhesus D antigen carrying a missense mutation, nor do Westhoff *et al.* teach or suggest a nucleic acid molecule encoding a human RHD antigen having a missense mutation contributing to or indicative of the weak D phenotype. Salvignol *et al.* do not describe a nucleic acid molecule encoding a human Rhesus D antigen, nor do Salvignol *et al.*, teach or suggest a nucleic acid molecule encoding a human RHD antigen having a missense mutation or a missense mutation contributing to or indicative of the weak D phenotype. Cherif-Zahar *et al.* do not describe a nucleic acid molecule encoding a human RHD antigen, nor do Cherif-Zahar *et al.* teach or suggest a nucleic acid molecule encoding a human RHD antigen having a missense mutation or a missense mutation contributing to or indicative of the weak D phenotype.

Sambrook *et al.* fails to provide that which is missing from Westhoff *et al.*, Salvignol *et al.* and Cherif-Zahar *et al.* Sambrook *et al.* do not teach or suggest a nucleic acid molecule encoding a human Rhesus D antigen, a nucleic acid molecule encoding a human RHD antigen

having a missense mutation or a nucleic acid molecule encoding a human RHD antigen having a missense mutation contributing to or indicative of the weak D phenotype.

Thus, absent any teaching or suggestion of the invention of claim 48, the claims would not have been obvious at the time of the invention in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection of claim 48 under 35 U.S.C. §103(a) over Westhoff *et al.*, Salvignol *et al.*, Cherif-Zahar *et al.* in view of Sambrook *et al.* be withdrawn.

The rejection of claim 48 under 35 U.S.C. §103(a) as allegedly unpatentable over LeVan *et al.* (correct cite is Westhoff *et al.*), Salvignol *et al.* (Biochem. Genet. 32:201 (1994) or Cherif-Zahar *et al.* (Proc. Natl. Acad. Sci. USA 87:6243 (1990)) each in view of U.S. Patent No. 6,200,802 (the '802 patent) is respectfully traversed. The Examiner indicates that the secondary reference '802 patent adds the limitation missing from the primary cited references as to claim 48, thereby allegedly rendering claim 48 obvious.

Claim 48 depends from claim 14 which, as set forth above, would not have been obvious in view of any of Westhoff *et al.*, Salvignol *et al.* or Cherif-Zahar *et al.* and Sambrook *et al.* alone, or in any combination.

The '802 patent fails to provide that which is missing from Westhoff *et al.*, Salvignol *et al.* and Cherif-Zahar *et al.* In particular, the '802 patent does not teach or suggest a nucleic acid molecule encoding a human Rhesus D antigen, a nucleic acid molecule encoding a human RHD antigen having a missense mutation or a nucleic acid molecule encoding a human RHD antigen having a missense mutation contributing to or indicative of the weak D phenotype. Thus, absent any teaching or suggestion of the invention of claim 48, the claims would not have been obvious at the time of the invention in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection of claim 48 under 35 U.S.C. §103(a) over Westhoff *et al.*, Salvignol *et al.*, Cherif-Zahar *et al.* in view of U.S. Patent No. 6,200,802 be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1 to 12, 14 and 48 to 51 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 03-3975.

Respectfully submitted,

Date: 2-25-02

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